

Treating Women Who Are Pregnant and Parenting for Opioid Use Disorder and the Concurrent Care of Their Infants and Children: Literature Review to Support National Guidance

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Objectives: The prevalence of opioid use disorder (OUD) during pregnancy is increasing. Practical recommendations will help providers treat pregnant women with OUD and reduce potentially negative health consequences for mother, fetus, and child. This article summarizes the literature review conducted using the RAND/University of California, Los Angeles Appropriateness Method project completed by the US Department of Health and Human Services Substance Abuse and Mental Health Services Administration to obtain current evidence on treatment approaches for pregnant and parenting women with OUD and their infants and children.

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Methods: Three separate search methods were employed to identify peer-reviewed journal articles providing evidence on treatment methods for women with OUD who are pregnant or parenting, and for their children. Identified articles were reviewed for inclusion per study guidelines and relevant information was abstracted and summarized.

Results: Of the 1697 articles identified, 75 were included in the literature review. The perinatal use of medication for addiction treatment (MAT, also known as *medication-assisted treatment*), either methadone or buprenorphine, within comprehensive treatment is the most accepted clinical practice, as withdrawal or detoxification risks relapse and treatment dropout. Medication increases may be needed with advancing pregnancy, and are not associated with more severe neonatal abstinence syndrome (NAS). Switching medication prenatally is usually not recommended as it can destabilize opioid abstinence. Postnatally, breastfeeding is seen as beneficial for the infant for women who are maintained on a stable dose of opioid agonist medication. Less is known about ideal pain management and postpartum dosing regimens. NAS appears generally less severe following prenatal exposure to buprenorphine versus methadone. Frontline NAS medication treatments include protocol-driven methadone and morphine dosing in the context of nonpharmacological supports.

Conclusions: Women with OUD can be treated with methadone or buprenorphine during pregnancy. NAS is an expected and manageable condition. Although research has substantially advanced, opportunities to guide future research to improve maternal and infant outcomes are provided.

Key Words: fetus, infant, neonatal abstinence syndrome, opioid, pregnancy, substance use disorder

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Opioid use disorder (OUD) is a chronic disease with potentially serious negative consequences for individuals—particularly so for pregnant and parenting women and their children—and society. (This document uses the current definition of *opioid use disorder* found in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, published by the American Psychiatric Association in

TABLE 1. Agencies and Offices Participating in the Federal Steering Committee

Bureau of Prisons (BOP)
Centers for Disease Control and Prevention (CDC)
Centers for Medicare & Medicaid Services (CMS)
Department of Defense (DoD)
Department of Veterans Affairs (VA)
Food and Drug Administration (FDA)
Health Resources and Services Administration (HRSA)
Indian Health Service (IHS)
National Institute on Drug Abuse (NIDA)
Office of National Drug Control Policy, The White House (ONDCP)
Office of the Assistant Secretary for Health (OASH)
Office of the Assistant Secretary for Planning and Evaluation (ASPE)
Office on Women's Health, Department of Health and Human Services (OWH)
Substance Abuse and Mental Health Services Administration (SAMHSA)

2013.) Since 2002, prescription opioid use and misuse has significantly increased among men and women (pregnant and nonpregnant) (Center for Behavioral Health Statistics and Quality [CBHSQ], 2015b). In 2013–2014, the number of women aged between 15 and 44 years who reported past-month non-medical use of psychotherapeutics, OxyContin (oxycodone) type, increased to 98,000, up 5.4% from 2011 to 2012. The number of women aged between 15 and 44 who reported past-month heroin use increased to 109,000 in 2013–2014, up 31% from 2011 to 2012 (CBHSQ, 2015a, Table 6.71A).

Infants exposed to tobacco, alcohol, prescription medications, and illicit substances may exhibit signs of physiologic withdrawal from these substances after birth. *Neonatal abstinence syndrome* (NAS) is a broad, nonspecific term assigned to this type of presentation in the newborn. It is widely applied both clinically and in the published literature to infants withdrawing from opioids. However, the more specific term *neonatal opioid withdrawal syndrome* (NOWS) is becoming more widely used. The utility of the more specific NOWS term is to capture more accurately the numbers of infants experiencing withdrawal from opioid exposure in utero. This is important because specific screening and treatment protocols can be used to promote the best outcomes for these infants, whereas infants not exposed to opioids may require different assessment and management. However, the published literature uses the more general NAS term and, in clinical practice, substance-exposed infants are typically exposed to multiple substances.

NAS incidence increased nearly 2-fold from 2009 to 2012 (Patrick et al., 2015). NOWS or NAS signs and symptoms occur 48 to 72 hours postbirth following discontinuation of prenatal opioid exposure (eg, Patrick et al., 2012; Jones and Fielder, 2015). Compared with pregnant women treated for OUD with methadone or buprenorphine, an untreated OUD group had more adverse maternal-fetal and maternal-infant health outcomes, including elevated risk of low-birth-weight newborns, intrauterine growth restriction, and placental changes (Binder and Vavrinková, 2008). Research to develop evidence-based criteria or consensus statements for the treatment of pregnant and parenting women with OUD and the concurrent care of their infants and children is largely absent.

Thus, practical recommendations derived from appropriate and accepted clinical experiences are urgently needed.

An effective method for assessing the validity of clinical procedures with limited scientific evidence is the RAND Appropriateness Method (RAM), developed in the 1980s by the RAND Corporation and the University of California, Los Angeles (UCLA). A PubMed search for “RAND/UCLA Appropriateness Method” indicates the RAM has been used in 127 articles, 77 of which were published in the last 5 years, including the American Society of Addiction Medicine (ASAM) *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use* (Kampman and Jarvis, 2015) and the *Practice Guidance for Buprenorphine for the Treatment of Opioid Use Disorders: Results of an Expert Panel Process* (Farmer et al., 2015).

The foundation of any appropriateness study is a critical literature review. However, unlike a meta-analysis, which combines the results of different studies to allow for the use of inferential statistical methods, the RAM literature review objective is to produce a synthesis of all available evidence, including the collective judgment of expert opinions, on a particular topic. The RAM literature review is typically less strict in inclusion criteria than a Cochrane review and, where evidence is lacking, may include lower-quality evidence, such as cohort or case studies (see Fitch et al., 2001, for RAM methodology details).

The RAM literature review presented in this article was undertaken for the US Department of Health and Human Services (HHS), Substance Abuse and Mental Health Services Administration (SAMHSA). SAMHSA used the RAM to assess the appropriateness of clinical procedures to treat pregnant and parenting women with OUD and their children and to ultimately develop guidance for healthcare providers who evaluate and treat this population.

As part of the RAM, SAMHSA convened a Federal Steering Committee (Table 1) and an Expert Panel (Table 2). The Federal Steering Committee and the Expert Panel recommended and evaluated the literature (see Search Method 3).

This literature review, which arose as part of the RAM process, is intended primarily for researchers and policy-makers in the areas of OUD and pregnant women whose opioid exposure also exposed infants in utero. In addition, healthcare providers interested in reviewing the evidence for treating such women and their infants and children will find this review useful.

Together, this literature review and the SAMHSA RAM report provide the foundation for a critically needed guidance

TABLE 2. Composition of Expert Panel by Field

Field of Expertise	Number of Expert Panelists
Family medicine	1
Neonatal medicine	1
Nursing	1
Obstetrics/gynecology	3
Pediatrics	1
Psychiatry	1
Psychology	1

document (hereafter referred to as the *Guide*) that will include practical recommendations for assessing and treating pregnant and parenting women with OUD and their infants and children. (SAMHSA's detailed RAM process and results are described in the report entitled *Advancing the Care of Pregnant and Parenting Women With Opioid Use Disorder and Their Infants: A Foundation for Clinical Guidance*, available at <https://www.regulations.gov/document?D=SAMHSA-2016-0002-0001>) The *Guide*, which is intended for healthcare providers, will be published by SAMHSA after a period of public review and comment.

The current literature review has 4 aims: (1) to summarize current evidence on treatment approaches for pregnant and parenting women with OUD and their children; (2) to identify the current state of the research; (3) to identify gaps in the research evidence; and (4) to derive recommended questions to guide future research.

METHODS

The RAM process took place from May through September 2015. Given the methodology used for this analysis, the research did not meet criteria for institutional review board review. SAMHSA instructed the Federal Steering Committee and the Expert Panel to recommend articles for inclusion in the literature review that were specific to treatment of pregnant or parenting women with OUD. Thus, articles pertaining to tobacco or alcohol cessation recommendations during pregnancy were not included. Additionally, the literature review excluded topics lacking literature; for example, treatment for depression or anxiety in pregnant or parenting women with OUD, or maternal, fetal, and child safety and efficacy data in the United States regarding naltrexone use in pregnant or postpartum women with OUD. The first step of the RAM process is to conduct a literature review of historical and newly published research. The RAM literature review took place between April 2013 and April 2015.

This RAM literature review used 3 separate search methods (Fig. 1) to identify peer-reviewed journal articles providing evidence on treatment methods for pregnant or parenting women with OUD, and for their children. Excluded were (1) review articles, as the literature review focused on primary research publications; (2) commentaries; and (3) articles not focused on opioid use and misuse in pregnant women or the effects of prenatal OUD on children (both immediate and long-term effects).

Search Method 1: Use of Bibliographies From Guidelines

For the first search method, relevant peer-reviewed primary research articles were extracted from the bibliographies of guidelines shown in Table 3, as well as recent compilations of materials devoted to substance use disorders and their treatment among pregnant or parenting women, and neonatal withdrawal from psychoactive substances.

A total of 404 articles were identified in the guidelines and bibliographies. Articles that were cited more than once were considered "critical articles" and were selected for inclusion, resulting in 29 articles. These articles may have included self-

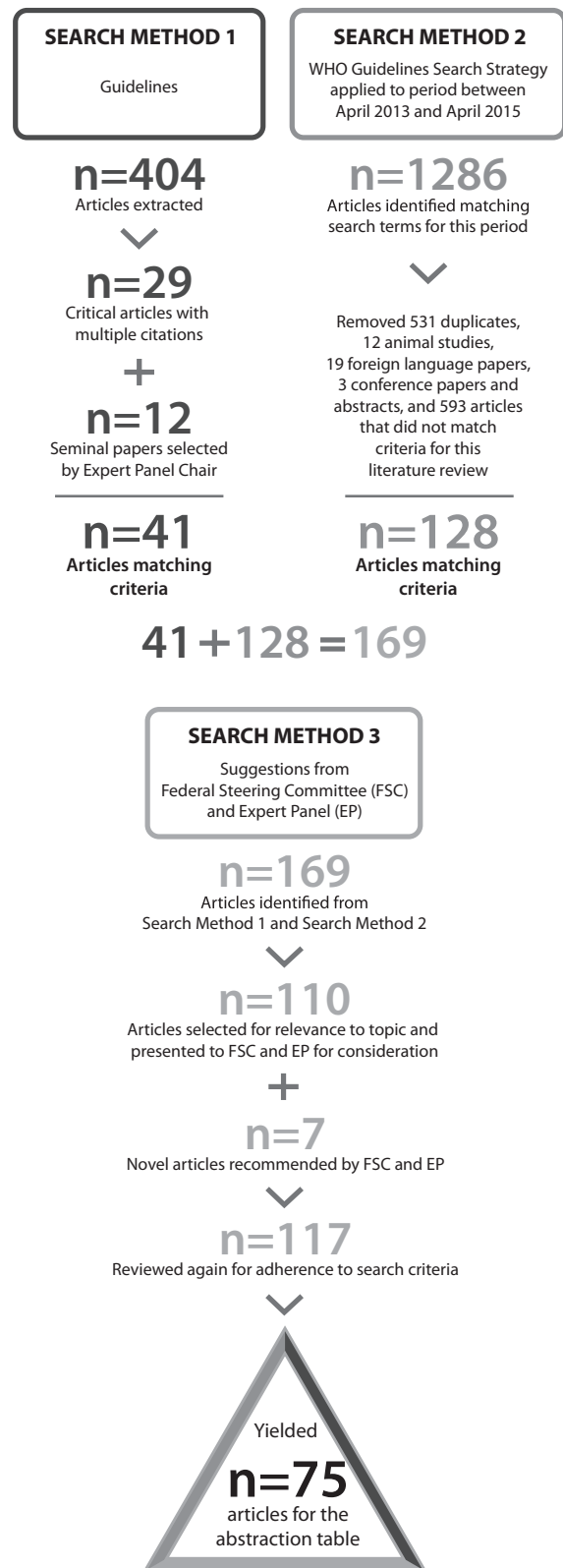


FIGURE 1. Flowchart of article identification and exclusion.

TABLE 3. Materials Used to Inform Search Method 1

American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women; American Society of Addiction Medicine. Committee Opinion No. 524: Opioid Abuse, Dependence, and Addiction in Pregnancy, 2012. Available at: https://www.acog.org/-/media/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/co524.pdf?dmc=1&ts=20160302T1440499290
American Society of Addiction Medicine. <i>National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use</i> . Available at: http://www.asam.org/quality-practice/guidelines-and-consensus-documents/npg
Hudak ML, Tan RC; Committee On Drugs, Committee On Fetus And Newborn, American Academy of Pediatrics. Clinical report: neonatal drug withdrawal. <i>Pediatrics</i> 2012;129:e540–e560. Available at: http://pediatrics.aappublications.org/content/129/2/e540
Reece-Stremtan S, Marinelli KA; The Academy of Breastfeeding Medicine. ABM Clinical Protocol #21: guidelines for breastfeeding and substance use or substance use disorder, revised 2015. <i>Breastfeed Med</i> 2015;10:135–141. Available at: http://www.bfmed.org/Media/Files/Protocols/Guidelines%20for%20Breastfeeding%20and%20Substance%20Use%20or%20Use%20Disorder.pdf
World Health Organization. <i>Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy</i> . Geneva, Switzerland: WHO Press; 2014. Available at: http://www.who.int/substance_abuse/publications/pregnancy_guidelines/en/

citations, but this was not analyzed. Of these 29 articles, 2 were cited 5 times, 4 were cited 4 times, 3 were cited 3 times, and 20 were cited twice. The titles and abstracts of the articles cited only once were also reviewed by the Expert Panel Chair to identify additional essential articles, resulting in 12 additional articles being selected for inclusion in this literature review. This method yielded 41 articles for in-depth review.

Search Method 2: Use of World Health Organization Search Method

To identify additional articles published between April 2013 and April 2015, the second search method replicated the literature search method used in the World Health Organization's (WHO's) *Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy* (WHO, 2014). The initial search produced 467 articles. A research librarian modified and added to the WHO search terms to identify additional relevant articles. Consistent with the WHO method, the librarian searched PubMed, PsycInfo, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Embase, and CENTRAL (Cochrane Center Register of Controlled Trials) databases using the listed search terms (see Appendix A, <http://links.lww.com/JAM/A53>).

This search method yielded 819 articles. Combining the 2 strategies produced a total of 1286 articles. Of those, 1158 articles were excluded, yielding 128 articles from search method 2.

Search Method 3: Federal Steering Committee and Expert Panel Literature Review

The 169 articles from search methods 1 and 2 were then reviewed independently and in depth for a second time for relevance to the topic of OUD in pregnant and parenting women. This review reduced the article total from 169 to 110.

The Federal Steering Committee and the Expert Panel reviewed the list of 110 articles. Federal Steering Committee members recommended a review of National Institute on Drug Abuse grantee publications from April 2013 to April 2015. That review identified 74 articles, of which 46 were novel articles not identified using the first 2 search methods. The Federal Steering Committee and Expert Panel members also recommended including another 12 articles. Of these 58 articles, 7 met eligibility criteria, yielding a total of 117 articles.

A final overview of the 117 articles was conducted to remove duplicate results and articles with insufficient numbers

of subjects or inappropriate use of statistical methods. Forty-two articles were dropped, leaving a final list of 75 articles (see Appendix B, <http://links.lww.com/JAM/A54>) selected to identify relevant evidence regarding treatment of pregnant and parenting women with OUD and their infants and children.

Creating the Abstraction Table

Three public health doctoral students with experience in conducting systematic literature reviews independently read the 75 articles. They abstracted relevant information from the eligible articles to generate a summary table presenting the key details of the study design and major findings (see Supplemental Material, <http://links.lww.com/JAM/A51>). To ensure fidelity to the process, the students began with a review of 3 articles. Their independent reviews resulted in complete agreement with regard to which data to extract. They then divided the remaining articles and worked collaboratively to create the abstraction table. The Expert Panel members then reviewed the abstraction table to inform their initial RAM literature review judgments.

RESULTS

All articles found through any of the search methods were included in the initial review. The earliest article was published in 1975, the latest in 2015. Included were 5 guidelines (see Table 3) that summarized the state of the field through early 2015. Of the 1697 articles identified, 75 were included in the literature review. This final list of 75 articles was selected to identify relevant evidence regarding treatment of pregnant and parenting women with OUD and their infants and children.

The current literature review covers 3 overlapping areas: (1) prenatal, (2) postnatal, and (3) neonatal. Most literature addresses methadone and buprenorphine, with limited data regarding buprenorphine + naloxone (Debelak et al., 2013; Jones et al., 2013a).

Prenatal

Medication-Assisted Withdrawal

Medication-assisted withdrawal is known to have a high relapse rate (Jones et al., 2008b). The subsequent return to use of illicit opioids subjects pregnant women and the fetus to all the risks associated with such psychoactive substance use (eg, Kaltenbach et al., 1998; Mattick et al., 2009). Despite this

concern regarding opioid use relapse, a secondary data analysis reported that a few studies support the concept that a small minority of women (16%) are successful at completing medication-assisted withdrawal and remaining in drug-free treatment until delivery (eg, Lund et al., 2012).

Medication for Addiction Treatment (MAT) (also known as medication-assisted treatment) and the Fetus

Opioid agonists cross the placental barrier (Zharikova et al., 2007) in concentrations consistent with maternal dose (Concheiro et al., 2010; de Castro et al., 2011), and may adversely affect the fetus. Given the inability to measure fetal physiologic behavior directly, fetal impact from opioid agonists has focused on measures of heart and movement activity. In a secondary data analysis from the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study, a large-scale trial comparing maternal and neonatal outcomes in 175 pregnant women randomly assigned to methadone or buprenorphine pharmacotherapy and provided with comprehensive care throughout their pregnancy, Jansson et al. (2011) found that compared with methadone-exposed fetuses, buprenorphine-exposed fetuses had significantly higher levels of fetal heart rate variability, more fetal heart rate accelerations, and greater coupling between fetal heart rate and fetal movement. Compared with the methadone-exposed group at 24 and 28 weeks' gestation, the buprenorphine-exposed fetuses displayed significantly less motor activity suppression and longer duration of movements than the methadone-exposed fetuses. In another secondary analysis of MOTHER study data, Salisbury et al. (2012) reported that, at 31 and 33 weeks of gestation, compared with buprenorphine-exposed fetuses, methadone-exposed fetuses were more likely to have a *nonreactive* (abnormal) nonstress test, fewer fetal heart rate accelerations, and lower biophysical profile scores (hence, more negative) at peak dosing. These findings suggest more optimal fetal indicators with buprenorphine than with methadone. These indicators were equivalent in the 2 groups of fetuses before dosing, suggesting that the medication was the only critical variable.

Kakko et al. (2008) prospectively followed buprenorphine-exposed pregnancies compared with retrospective methadone-exposed pregnancies. Their data support a greater incidence of intrauterine growth restriction in the methadone-exposed than in the buprenorphine-exposed fetuses, a conclusion based on a nonsignificantly higher number of cesarean deliveries in the methadone-exposed than the buprenorphine-exposed group.

Finally, Jansson et al. (2012) reported that—in a prospective sample of women undergoing 36-week fetal monitoring—fetal heart rate, fetal heart rate variability, and fetal activity were lower in methadone-exposed fetuses relative to the nonpsychoactive-substance-exposed fetuses, measured at peak dosage levels of methadone. Moreover, fetal movement at *trough* (just before maternal methadone dose) measurement was significantly lower in the methadone-exposed fetuses than in the fetuses who were not exposed to psychoactive substances, which was interpreted as a methadone persistent effect.

With regard to fetal heroin and methadone exposure, 2 studies provide conflicting results and conclusions. A meta-

analysis suggests that continued use of heroin while receiving methadone counteracts the birth-weight advantage gained from methadone alone (Hulse et al., 1997). In contrast, a cohort study suggests that methadone remains advantageous for the maternal-fetal dyad regardless of continued heroin use (Buckley et al., 2013). In a surveillance study, methadone alone has also not been shown to increase fetal or infant mortality (Kelly et al., 2012).

Postnatal

Methadone and Buprenorphine: Pain Medication During Pregnancy, Delivery, and Postpartum

Individuals with long-term exposure to opioids experience *tolerance* (reduced analgesia) and *hyperalgesia* (increased sensitivity to pain) (Savage, 1996). Therefore, pregnant and postpartum women using MAT or with a history of long-term exposure to opioids will likely need higher doses of opioid agonist medication during labor, delivery, and the postpartum period (Alford et al., 2006; Meyer et al., 2007, 2010). Furthermore, opioid agonist-antagonist medications (eg, nalbuphine or butorphanol) should be avoided owing to the risk of precipitated withdrawal in women receiving opioid agonists (eg, methadone or buprenorphine) (Savage, 1996; Cassidy and Cyna, 2004; Jones et al., 2014b). Jones et al. (2009) examined postpartum pain management in women with severe OUD in the Pregnant and the Reduction of Opiates: Medication Intervention Safety and Efficacy (PROMISE) study, a small-scale trial comparing maternal and neonatal outcomes in 30 pregnant women randomly assigned to methadone or buprenorphine pharmacotherapy. On average, buprenorphine-receiving women decreased their daily ibuprofen dose, whereas methadone-receiving women increased their daily ibuprofen dose.

Methadone and Buprenorphine: Postpartum Dosing

It is well established that women need increases in methadone dose with advancing gestation (eg, Jones et al., 2005). A similar yet less conclusive pattern is seen with buprenorphine (eg, Jones et al., 2005). Dividing the dose of methadone in half (split dosing) is an approved protocol for women in the third trimester of pregnancy because of the shorter half-life and larger clearances of medications during pregnancy (eg, Bogen et al., 2013). There is mixed evidence supporting the need to lower methadone or buprenorphine doses after delivery (Jones et al., 2008a; Bogen et al., 2013; Pace et al., 2014; Bastian et al., 2016).

Methadone and Buprenorphine: Breast Milk

Limited research has focused on concentrations of opioid agonist medication in breast milk; firm conclusions are difficult given the generally small sample sizes. However, assays clearly suggest that concentrations of both buprenorphine (eg, Ilett et al., 2012) and methadone (eg, Jansson et al., 2008b) in human breast milk are quite low, and pose little risk for neonates.

Methadone and Buprenorphine: Breastfeeding

Women maintained on a stable dose of methadone or buprenorphine should be encouraged to breastfeed (WHO,

2014) unless specifically contraindicated (eg, maternal human immunodeficiency virus positive [HIV+]). Few studies of opioid agonist pharmacotherapy for pregnant women with OUD have focused on breastfeeding as an outcome (notably, Johnson et al., 2001; Abdel-Latif et al., 2006; Abrahams et al., 2010; Debelak et al., 2013). The US literature typically shows low rates of breastfeeding among postpartum women with OUD (eg, Jansson et al., 2008a; Jones et al., 2010b; Pritham et al., 2012).

Impact of Breastfeeding

A study of neonates prenatally exposed to methadone or buprenorphine for a minimum of 30 days found that breastfed neonates had significantly shorter lengths of hospital stay and need for pharmacotherapy for NAS (Wachman et al., 2013). Abdel-Latif et al. (2006) examined the impact of breastfeeding in a retrospective chart review of women with opioid dependence (not all of whom were maintained on methadone; none were maintained on buprenorphine), who either breastfed or formula fed their neonates on day 5 of life. The breastfed neonatal group had lower withdrawal scores for the first 9 days postpartum, a lower rate of need for pharmacotherapy for withdrawal, a longer median time to such pharmacotherapy, and shorter hospital stays. Although relevant research is inconclusive, breastfed neonates may be exposed to small amounts of either buprenorphine or methadone, thereby avoiding the withdrawal symptoms that might be caused by an abrupt cessation of opioid exposure (Malpas and Darlow, 1999). It has also been postulated that NAS severity is mitigated by the act of breastfeeding rather than the amount of medication in breast milk (eg, WHO, 2014).

Methadone and Buprenorphine: NAS Measurement and Treatment Incidence

Widely different NAS prevalence rates are reported in the research, which largely consists of retrospective cohort studies (see Jones et al., 2012, for a comprehensive buprenorphine review). These discrepancies are likely due to 4 factors. First, the studies have different inclusion criteria (eg, including women who were using benzodiazepines), and inclusion and/or exclusion criteria for nonrandomized studies were often not reported (Jones et al., 2012). Second, there is wide variability in the measurement of NAS. For example, many scoring systems, such as the modified Finnegan, allow clinicians to assess the severity of NAS. However, as with all behavioral measures, such Finnegan scores are fallible; moreover, interrater reliability has often been reported to be poor or substandard. Although the Finnegan scoring system is used to assess opioid and nonopioid withdrawal, shortened or simplified versions of this scoring system have not been widely adopted (Kocherlakota, 2014). Third, examiners' skills vary. For example, the Finnegan scoring system requires considerable training for reliable use, yet even trained raters have difficulty accurately judging some items, such as the difference between "mild" and "marked" tremors (Jones and Fielder, 2015). Fourth, there are differences in NAS treatment initiation and weaning protocols, because the healthcare provider needs to customize each infant's treatment to reflect withdrawal intensity and gestational period (Kocherlakota,

2014). Additionally, initiation of treatment and weaning of medications will differ depending on the standardized scoring system used and the protocol used (Teague et al., 2015). The current consensus is that the NAS incidence is similar for buprenorphine and methadone, at approximately 50%. Moreover, research indicates that compared with methadone-exposed neonates, buprenorphine-exposed neonates require less morphine to treat NAS, spend less time in the hospital medicated for NAS, and have a shorter hospital stay (Jones et al., 2005, 2010b, 2012).

Methadone and Buprenorphine: Maternal Dose-response Relationships to Neonatal Outcomes

Retrospective studies examining the relationship between methadone dose (and, to a lesser extent, buprenorphine dose) and neonatal outcomes have yielded inconsistent findings (see Jones et al., 2013c, 2014a, for reviews of these 2 lines of research). The need to examine whether there was a relationship between dose and neonatal outcomes was stimulated by the concern that higher methadone doses might harm the fetus and result in more severe NAS. Jones et al. (2013c, 2014a) used MOTHER data and found no relationship between either methadone or buprenorphine dose and peak NAS score, total amount of morphine needed to treat NAS, duration of neonatal hospital stay, duration of pharmacotherapy for NAS, estimated gestational age at delivery, Apgar score at 5 minutes, and neonatal head circumference, length, and weight at birth. These findings on the lack of a link between methadone or buprenorphine dose and NAS extend the results of a meta-analysis (Cleary et al., 2010) that found that the severity of NAS was unrelated to methadone dose, and strongly suggest that the practice of reducing maternal opioid agonist medication to protect the fetus is unwarranted.

Weight-Based Versus Symptom-Based Pharmacotherapy for NAS

Beginning with Finnegan et al.'s (1975) guidance regarding weight-based pharmacotherapy for NAS, treatment for NAS has been weight based with few exceptions (notably the Jones et al., 2010b, MOTHER study). However, pharmacotherapeutic dosing for NAS based on symptom severity may be more efficacious than pharmacotherapeutic dose based on neonatal weight (Jansson et al., 2009). At present, the dosing regimen is thought to be complex, and dependent on both initial assessment of NAS severity and response to treatment.

Methadone and Buprenorphine: NAS Signs and Time Course

Gaalema et al. (2012) compared the NAS signs of methadone-exposed and buprenorphine-exposed infants in the MOTHER study, who had been assessed for 10 days following delivery using the study's modified Finnegan scale (MOTHER NAS Scale [MNS]; Jones et al., 2010b). The authors found that undisturbed tremors and hyperactive Moro reflex occurred significantly more often in the methadone-exposed neonatal group, and nasal stuffiness, sneezing, and loose stools occurred significantly more often in the buprenorphine-exposed neonatal group. The methadone-exposed group had higher mean MNS scores than did the buprenorphine-

exposed neonatal group, marked by higher scores on disturbed and undisturbed tremors, hyperactive Moro reflex, excessive irritability, and failure to thrive; sneezing was significantly higher among buprenorphine-exposed neonates. Gaalema et al. (2013) also found that in a secondary data analysis the mean time (hours:minutes, interquartile range) to initiation of pharmacotherapy for buprenorphine-exposed neonates was significantly longer compared with methadone-exposed neonates (71:02, 44:21–96:27 vs 34:12, 21:00–55:41, respectively, $P < 0.001$), a finding consistent with the MOTHER study and a previous smaller trial (Fischer et al., 2006). The American Academy of Pediatrics recommendation that both groups of neonates be monitored for NAS for a minimum of 5–7 days (120–168 hours) was crafted to ensure that no infant is sent home too early to determine whether NAS treatment is needed (Hudak and Tan, 2012).

Other Factors Affecting NAS

A number of studies have focused on elucidating the factors that exacerbate or minimize NAS. The extent of nicotine use has been found to be a robust factor in increasing NAS expression (eg, Jones et al., 2013b). Furthermore, the presence of selective serotonin reuptake inhibitors and/or benzodiazepines may also exacerbate NAS expression (Kaltenbach et al., 2012).

Rooming-in to Reduce NAS

Recent research suggests that the first-line approach to managing neonates prenatally exposed to 1 or more classes of opioids may be a rooming-in model that minimizes stimulation from outside sources (eg, by using low lighting), maximizes maternal-infant contact, and encourages breastfeeding (eg, Abrahams et al., 2010).

Measurement of NAS

Several studies have attempted to develop alternative measures to the Finnegan scoring system, also referred to as the Neonatal Abstinence Scoring System (NASS). Moreover, many of the measures in clinical use are modifications of the NASS, making comparisons among cohort studies difficult if not impossible. The psychometric properties of both the NASS and the MNS certainly seem deficient (Jones et al., 2016c), suggesting a need to develop new NAS measures. (See Jones and Fielder, 2015, for a review of these measures and the issues in the measurement of NAS.) Research aimed at developing short forms of the NASS and the MNS that are easier to administer consistently has shown promise (eg, Jones et al., 2010a, 2016b).

NAS Medication Treatment Protocol

Paregoric was originally the treatment of choice for NAS; it is found in the initial treatment protocol presented by Finnegan et al. (1975). Diluted tincture of opium was also once popular, but concerns about its high alcohol content and the possibility of its confusion with deodorized tincture of opium (both are commonly abbreviated DTO) led to calls for use of oral morphine sulfate instead. Oral morphine sulfate was found to be as efficacious as diluted tincture of opium in a randomized controlled trial (Langenfeld et al., 2005). Oral

morphine use has been complicated by a retrospective review suggesting that methadone may be just as efficacious (Lainwala et al., 2005). Buprenorphine holds promise as a first-line NAS treatment (eg, Kraft et al., 2008, 2011).

Although research indicates that clonidine or phenobarbital may be used as second-line medications for infants with more severe NAS not completely controlled with morphine or methadone (eg, Coyle et al., 2002; Agthe et al., 2009), ongoing research is still trying to determine the safety and efficacy of clonidine (Bada et al., 2015).

Future Research Topics

This RAM literature review highlights the complexity of issues and practices affecting the treatment of pregnant and parenting women for OUD and the concurrent care of their infants and children. Ongoing research on the prenatal, postnatal, and neonatal periods is needed. To that end, the chair of the Expert Panel, Hénriette E. Jones, PhD, a senior author of this article, in collaboration with SAMHSA staff drew up a list of future research topics, presented in Table 4. The selected topics have been the subject of promising but not yet definitive research. Although not exhaustive, the table highlights important areas for future study that might lead to meaningful advances in the care and outcomes of mothers who have OUD and their children.

CONCLUSIONS

The number of women aged between 15 and 44 who reported past-month nonmedical use of psychotherapeutics, OxyContin (oxycodone) type, and the number of women aged between 15 and 44 who reported past-month heroin use increased from 2011–2012 to 2013–2014 (CBHSQ, 2015a, Table 6.71A). In addition, the prevalence of OUD during pregnancy more than doubled between 1998 and 2011, to 4 per 1000 deliveries (Maeda et al., 2014). Given that women with OUD have a higher frequency of additional risk factors for adverse pregnancy outcomes than do pregnant women who do not use opioids, evidence-based clinical guidance on the treatment of these women and their children is needed. The present article, developed as part of a RAM process, serves as the basis for a series of recommendations for researchers and policymakers in the areas of OUD and pregnant women whose opioid exposure also exposed infants in utero. Healthcare providers interested in reviewing the evidence for treating such women and their infants and children may also find this review useful. This work supports and extends the ASAM *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use*, which includes guidance on treating pregnant women (Kampman and Jarvis, 2015).

Several recent reviews have similarly discussed use of prescription opioids during pregnancy and birth outcomes. Zedler et al. (2016) found evidence that buprenorphine treatment for OUD during pregnancy demonstrates lower risk of preterm birth, greater birth weight, and larger head circumference compared with methadone treatment. Yazdy et al. (2015) found evidence that head circumference and birth length have no association with opioid use. (The present status of research does not indicate that opioid agonist

TABLE 4. Questions for Future Research

Domain	Future Research Questions
<p>MATERNAL (across all 4 trimesters) Substance use disorders</p>	<p>What level of substance use is harmful to the mother, fetus, and child (eg, Wright et al., 2016)?</p> <p>What are the potential pretreatment and/or treatment, fetal, neonatal, and child outcomes between women with OUD who misuse prescription opioids and become pregnant compared with women with OUD who use illicit opioids and become pregnant?</p> <p>What are the best methods for detecting emerging trends in substance use and prenatal exposure to substances (eg, Martin et al., 2015)?</p> <p>To what extent is genomics testing helpful as a component of OUD identification? If found to be helpful, how should it be used?</p> <p>What are the best methods for supporting women with OUD who are seeking treatment?</p> <p>How can structural barriers that inhibit women from seeking, entering, and/or engaging in treatment be overcome?</p> <p>What are the best ways to treat women for OUD in rural settings across all 4 trimesters (eg, Jumah et al., 2015; Meyer and Phillips, 2015)?</p> <p>What are the best ways to prevent OUD? What are the unique factors and effective program elements for women?</p> <p>Which methods of contraception work best for which women with OUD (considering the likelihood of trauma history) and how can they be made more accessible (eg, Terplan et al., 2015)?</p> <p>Which behavioral interventions (such as contingency management) are most effective for pregnant and parenting women with OUD? What internal and external factors explain differences in effectiveness (eg, type of pharmacotherapy, other maternal variables)?</p> <p>To what extent can contingency management be implemented in clinical settings to help women across all 4 trimesters improve outcomes (eg, Forray, 2016)?</p> <p>What are the most cost-effective ways to provide care for women with OUD that will lead to optimal maternal and child outcomes?</p> <p>What are the best reimbursement structures for promoting engagement of and access, treatment, and optimal outcomes for women with OUD and their children?</p>
<p>For co-occurring health and social issues</p>	<p>What are the best methods to ensure universal hepatitis C and HIV screening and treatment for pregnant women with OUD (eg, Krans et al., 2016a, 2016b)?</p> <p>What are the best methods to identify and address social determinants of health in pregnant and parenting women with OUD?</p> <p>To what extent does tobacco influence outcomes for mother, fetus, and child in women receiving MAT across all 4 trimesters (eg, Akerman et al., 2015)?</p> <p>What are the best ways to treat comorbid conditions, including alcohol, benzodiazepine, stimulant, and marijuana use disorders, as well as tobacco use, depression, anxiety, posttraumatic stress disorder, HIV, hepatitis C, and sexually transmitted infections in pregnant women with OUD (eg, Coleman et al., 2015; Caputo et al., 2016; Chisolm and Payne, 2016; Huang et al., 2016; O'Connor et al., 2016)?</p> <p>What is the relative contribution of multiple risk factors to adverse outcomes? What are the resilience factors most likely to improve these outcomes (eg, Kramlich and Kronk, 2015)?</p>
<p>Screenings</p>	<p>What are the optimal screening tools and procedures to identify other types of SUDs in pregnant women with OUD (eg, Ondersma et al., 2015; Wright et al., 2016)?</p> <p>What are the best ways to treat women of different ages with SUD, and women who become pregnant while being treated with opioids for pain?</p> <p>What are the most effective tools and procedures for screening for OUD and other health and social issues in integrated care (eg, Goodman, 2015)?</p>
<p>Medication selection, induction, and dose adjustments</p>	<p>How should the optimal opioid agonist therapy be selected for pregnant and parenting women? What patient variables (eg, age, socioeconomic status, race, ethnicity) and community variables (eg, urban, suburban, rural, incarcerated) should be considered?</p> <p>Which opioid treatment regimen works best for pregnant patients using prescription opioids or heroin (eg, Martin and Finlayson, 2015; Krans et al., 2016a; Noormohammadi et al., 2016)?</p> <p>What are the best methods for induction onto buprenorphine during pregnancy (eg, Meyer and Phillips, 2015; Jones et al., 2016a)?</p> <p>What are the best methods for induction onto an optimal dose of methadone during pregnancy (eg, McCarthy et al., 2015)?</p> <p>To what extent does fetal stress during MAT induction occur and what are the implications of such stress for the child?</p> <p>What are the best strategies for maintaining a safe, effective dose of MAT over the course of a patient's pregnancy, postpartum period, and breastfeeding period?</p> <p>To what extent is naltrexone safe and effective for OUD for the maternal-fetal and/or maternal-infant dyad?</p> <p>Under what circumstances would transition from one form of MAT to another be beneficial to the mother-fetal, mother-infant dyad?</p> <p>What is the relative safety and efficacy of buprenorphine + naloxone vs buprenorphine or methadone during pregnancy? What is the risk/benefit of transferring a woman from buprenorphine + naloxone to another opioid agonist because of pregnancy? How should such a transition be accomplished (eg, Meyer et al., 2015; Nørgaard et al., 2015; Wiegand et al., 2015; Dooley et al., 2016; Zedler et al., 2016)?</p>
<p>PRENATAL</p> <p>Medically assisted withdrawal</p>	<p>Under what circumstances is medically assisted withdrawal appropriate for pregnant women and what medication should be used (eg, Dooley et al., 2015; Welle-Strand et al., 2015; Bell et al., 2016)? What accompanying services are required to ensure an optimal outcome for both mother and child?</p> <p>What are the best methods for identifying women who are most likely to successfully complete medication-assisted withdrawal and maintain abstinence?</p>
<p>Pain relief</p>	<p>What are the optimal pharmacological and nonpharmacological approaches to providing pain relief during pregnancy, labor, delivery, and the postpartum period for women receiving MAT?</p> <p>Which pain management protocols are most effective for reducing pain for which women with OUD during labor, delivery, and the postpartum period?</p>

TABLE 4 (Continued)

Domain	Future Research Questions
NEONATAL	
Screening for the presence of prenatal exposure to substances	<p>What are the best biological matrices and analytical methods for accurately determining neonatal exposure to opioids and other substances (eg, Joya et al., 2015; Kyle et al., 2015)?</p> <p>What are the best protocols to support the mother-child dyad and ensure the safety of child and mother?</p> <p>What are the best strategies to help women navigate legal issues and ensure that appropriate consent occurs?</p> <p>What are the extent and impact of polysubstance use on opioid exposure in pregnancy and NAS? In particular, what are the long-term effects of prenatal exposure to opioids, as compared with exposure to other substances or pharmaceuticals? Such research needs to be carefully controlled for social, familial, and environmental risk and protective factors encountered during childhood.</p>
Screening and assessment of NAS	<p>What are the most psychometrically sound screening and assessment measures of NAS for premature, term, and older infants (Jones and Fielder, 2015)?</p> <p>What are the best methods and tools for identifying, assessing, and treating possible comorbid withdrawal from other substances such as benzodiazepines, nicotine, or alcohol?</p> <p>What degree (amount and timing) of exposure to prescription opioids for pain should be considered a risk for NAS (eg, Desai et al., 2015)?</p> <p>How efficient, valid, and reliable are the new short forms of the MNS (eg, Jones et al., 2010a; Jones et al., 2016b)? Further research is needed.</p>
Treatment of infants for NAS	<p>What is the safest, most effective protocol for using nonpharmacological NAS treatments that will also minimize the ongoing medication exposure of infants with NAS (eg, Patrick et al., 2016)?</p> <p>What are the best items to include in the most accurate and sensitive measures of NAS (eg, Jones et al., 2010a; Jones et al., 2016b)?</p> <p>Which medications should be used as first-line therapy or considered second-line options for the treatment of NAS, and for which infants (eg, Nayeri et al., 2015; Young et al., 2015)?</p> <p>What are the best protocols for dosing and weaning neonates from NAS medications (eg, Hall et al., 2015b; Jones and Fielder, 2015; Patrick et al., 2016)?</p> <p>What are the pharmacokinetics and dynamics of NAS medications? How do they differ by medication and age of infant (Hall et al., 2015a; Ng et al., 2015; Wiles et al., 2015; Johnson et al., 2016)?</p> <p>What are the effects of co-occurring exposures to substances such as alcohol and other stressors on NAS severity (eg, Kreitinger et al., 2016; Popova et al., 2016)?</p> <p>To what extent do maternal or infant factors alone or in combination exacerbate and mitigate NAS and its severity (such as tobacco use, prematurity, and genetics) (eg, Ruwanpathirana et al., 2015; Stover and Davis, 2015)?</p> <p>What medication might be more efficacious for long-acting vs short-acting opioids when treating infants for NAS?</p> <p>Would neonates of mothers maintained on an opioid agonist medication respond better to that same medication, or would oral morphine or another medication be a better choice?</p> <p>What are optimal pharmacotherapeutic dosings for NAS based on symptom severity?</p> <p>What are the most cost-effective ways to produce the best outcomes and care for infants with NAS (eg, Brandt et al., 2015)?</p>
POSTNATAL	
Relapses	<p>What are the factors and predictors for transitioning to another medication a new mother who was stable on MAT and relapses (Forray et al., 2015)?</p>
Breastfeeding	<p>How should breastfeeding amount (eg, exclusivity or supplemented with formula) and duration be differentiated by OUD treatment medication (Tsai and Doan, 2016)?</p> <p>What are the best parameters and optimal duration for breastfeeding (eg, expressed, supplemented with formula, standard) based on OUD treatment medication (Tsai and Doan, 2016)?</p> <p>To what extent is breastfeeding safe while the mother is using marijuana and/or other substances (eg, Chomchai et al., 2016)?</p> <p>How can the representation of pregnant and breastfeeding women best be increased in clinical trials (Scaffidi et al., 2016)?</p> <p>What are the most efficacious interventions to successfully introduce, and then maintain, breastfeeding in opioid-agonist-maintained new mothers?</p>
Mother-child dyad	<p>What parenting and recovery supports are most beneficial to the maternal-child dyad (eg, Giles et al., 2016)? What family, maternal, child, or community variables need to be considered? What is the optimal frequency and duration of delivery for such services? What is the optimal role of peer-support services?</p> <p>What are the modifiable maternal variables that can mitigate the risk of NAS for infants of women who, for medical reasons, require opioid therapy during pregnancy? Such variables include tobacco cessation and in-home support services.</p> <p>Which dyads will benefit from rooming in? Which dyads will benefit from outpatient treatment with medication for NAS (eg, Holmes et al., 2016)?</p> <p>What in-home early interventions or developmental assessments provide the greatest benefit to the infant? What family, maternal, child, or community variables need to be considered? What is the optimal frequency and duration of delivery for such services?</p> <p>What is the safest and most effective strategy for providing ongoing NAS medication posthospital discharge?</p> <p>How can sudden infant death syndrome (SIDS) and other causes of infant mortality be reduced in infants prenatally exposed to substances (Cohen et al., 2015; Ali et al., 2016)?</p> <p>To what extent does a prenatal opioid exposure environment lead to changes in fetal development and later developmental consequences (eg, Beckwith and Burke, 2015; Kivistö et al., 2015; Konijnenberg and Melinder, 2015; Pearson et al., 2015; Whitham et al., 2015; Jones et al., 2016a)?</p>

MAT, medication for addiction treatment; MNS, NASS or the MOTHER NAS Scale; NAS, neonatal abstinence syndrome; OUD, opioid use disorder; SUD, substance use disorder.

pharmacotherapy during pregnancy exposes the fetus to greater teratological risk than found in the non-opioid-exposed fetus; however, to date, no research has been reported indicating that MAT during pregnancy is associated with birth defects.) This RAM literature review is broader in scope than these recent reviews and makes a significant contribution to the literature by providing substantial recommendations for future research.

The present article summarized the results from 75 studies that focused on prenatal and postnatal OUD treatment of women and their prenatally opioid-exposed infants and children. The collective literature review points to several conclusions:

- Although withdrawal from opioids to an opioid-free state is possible during pregnancy, relapse rates are high and repeated cycles of intoxication and withdrawal are associated with possible adverse effects.
- The accepted treatment for OUD during pregnancy is long-acting opioid agonist MAT that includes methadone or buprenorphine provided within the context of a comprehensive program of obstetrical care and behavioral intervention.
- For the fetus, steady states of buprenorphine appear to have a less sedating effect than single daily dosing of methadone. Split dosing of methadone in the third trimester may also have a less suppressive effect on the fetus. At this time, the postnatal and longer-term effects of suppression of fetal parameters remain unknown.
- As gestation increases, higher doses of methadone and possibly buprenorphine appear to be needed.
- Postpartum women with OUD may need greater amounts of pain relief medication compared with women without such opioid experience.
- Breastfeeding among women not using other substances and maintained on methadone or buprenorphine can encourage and promote maternal-infant bonding, and likely have mitigating effects on NAS severity.
- NAS severity may be less with buprenorphine than with methadone; however, other factors such as maternal tobacco use, maternal benzodiazepine use, dyad genetics, NAS medication regimens, and hospital protocols determining where infants reside (eg, neonatal intensive care unit or rooming-in) may alter this relationship.

Although NAS has been an issue of focus, it is an identifiable and treatable condition that is only one aspect of the complete risk/benefit ratio decision for any patient and her provider to make during pregnancy. For a sustained recovery, the maternal-fetus/maternal-infant dyad must be considered as a whole and in the context of the dyad's risk and protective life factors.

The summary of research found in the present article must be considered within the context of its limitations. These include the fact that different literature search methods may find different articles and possibly lead to different conclusions. Several studies may have limited generalizability to the US population, in large part because of cultural and health system differences. Furthermore, the descriptive and

correlational designs of some studies may have resulted in several biases (eg, selection bias weakens the study results, confounding psychosocial factors).

Although this literature review identified evidence from recent clinical research studies providing support for the *Guide*, substantial questions for future research, as noted in Table 4, still remain. Further research that focuses on those questions is likely to have an impact on the treatment of pregnant and parenting women and their infants and children.

In conclusion, both methadone and buprenorphine provide effective treatment for OUD before, during, and after pregnancy; however, neither medication is a "cure." For the mother, both medications offer benefits to support behavioral change. For the fetus, buprenorphine appears less sedating than methadone. For the neonate, collective randomized controlled trials, and prospective and retrospective data, show a less severe NAS for buprenorphine than methadone exposure in utero. However, NAS is only one aspect of the complete risk/benefit ratio decision that must be made. Any MAT plan for OUD must be developed in the context of a comprehensive care program that is supportive of and responsive to women and the maternal-fetus/maternal-infant dyad.

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